Formulation and Evaluation of Oral Controlled Release Clarithromycin Matrix Tablets using Hydrophilic Polymer

T.N.K. Suriyaprakash¹, S. Lakshmana Prabu², A. Arumugarajan³ and A. Sumathi³

¹Dept of Pharmaceutics, Al Shifa College of Pharmacy, Perintalmanna, Kerala – 679322, ²Dept of Pharm. Technology, Anna University of Technology, Tiruchirappalli – 620024, India, and ³Dept of Pharmaceutics, Periyar College of Pharmaceutical Sciences, Trichy – 620021, Kerala, India.

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ABSTRACT

The objective of the present study was to develop clarithromycin tablets from polymeric hydrophilic matrices using methocel and characterization for its physic-chemical properties and in vitro release studies to optimize its release profile with the standard marketed product. Matrix tablets were prepared by wet granulation method using PVP and ethyl cellulose as binding agents. The matrix tablets were evaluated for its thickness, hardness, friability, weight variation, drug content and in vitro release studies. The drug delivery was analyzed using the paddle method in phosphate buffer pH 6.0 (dissolution medium I) and phosphate buffer pH 6.8 containing 0.5% sodium lauryl sulfate (dissolution medium II) and compared with USP dissolution limits. The dissolution release profile of formulation F9 was comparable with the market formulation and the difference factor and similarity factor f1 and f2 was found to be 2.44 and 83.18 in dissolution medium I; 1.44 and 89.71 in dissolution medium II. Stability studies were carried out as per ICH guidelines and tested for its physicochemical properties and in vitro studies. The study shows that the matrix method can be employed for preparing clarithromycin sustained release formulation using combination of hydrophilic polymers like Methocels and sodium carboxy methyl cellulose.

KEYWORDS: Clarithromycin; HPMC; Eudragit NE 30D; Sustained release matrix; Tablet disintegrant.

Introduction

The design of oral controlled drug delivery systems (CDDS) should be primarily aimed to achieve better predictability, reproducibility and increased bioavailability. Approximately 50% of the drug delivery systems available in the market are oral drug delivery systems and these systems have more advantage due to patient acceptance and ease of administration. The ideal drug delivery system should have the advantage of single dose for the whole duration of treatment and it should deliver the active drug directly at the specific site. Scientists have succeeded in developing a system that can be as near to an ideal system and it encourages the scientists to develop controlled release systems.

Controlled release implies the predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimization of the therapeutic effect of drug by controlling its release in the body with lower and less frequent dose (Roseman and Cardinelli, 1980). An important requisite for the successful performance of oral controlled release is that the drug should have good absorption throughout the GIT, preferably by passive diffusion to ensure continuous absorption of the released drug by incorporation of rate controlling hydrophilic polymer (Ranga Rao and Padmalatha Devi, 1988; Salsa et al., 1997; Lakshmana Prabu et al., 2009). A major constraint in oral controlled drug delivery is that not all drug candidates are absorbed uniformly throughout the GIT. Some drugs are absorbed in a particular portion of the GIT only or absorbed to a different extent in various segments of the GIT, such drugs are said to have an absorption window which identifies the drug’s primary region of absorption in the GIT.

The matrix system is commonly employed for preparing controlled release dosage forms because of its easy manufacturing process. The adjustment of the hydrophilic polymer concentration, various viscosity grades and the addition of different types and levels of excipients can modify the drug release rate (Ford et al., 1991; Sung et al., 1996; Siepmann et al., 1999).

Clarithromycin is a semi-synthetic broad spectrum macrolide antimicrobial agent commonly used for the treatment of mild to moderate infection caused by susceptible stains like Haemophilus influenza, Haemophilus parainfluenzae, Moraxella catarrhalis, Streptococcus pneumoniae, Chlamydia pneumonia and Mycoplasma pneumoniae. Its biological half-life has been reported as 3 - 4 h.

The objective of the present work was to formulate controlled release tablets of clarithromycin by wet granulation technique and evaluation for its pre-
Materials and Methods

Chemicals and Drug Materials

Clarithromycin was obtained as gift sample from Alembic Pharmaceuticals, Ahmedabad, India. HPMC, prime lose and lactose were obtained from DMV International. Sodium carboxy methyl cellulose from Reliance Chemical Co, Ethyl cellulose from Rohm Gmp & Co, Povidone from BASF Tech; Magnesium stearate, talc, aerosol, stearic acid and starch from Loba Chemie, Microcrystalline cellulose from Sigachi Chemicals and Colourants from Rohan Dye Chem.

Instruments and chromatographic conditions

The integrated high performance liquid chromatography system (Shimadzu HPLC Class 10A Series) with two LC-10AT pumps at a fixed wavelength guided by a programmable UV/Vis detector (SPD-10A) which was connected to a BDS- Hypersil RP-C18 column (250 X 4.6 mm i.d. particle size 5 μ) at 25°C temperature. The HPLC system was equipped with the software “Class LC-10AT series version 5.03” (Shimadzu). The mobile phase was a mixture of 0.067M phosphate buffer (pH 4.0) and methanol (65: 35% v/v) pumped at a flow rate of 1.0 ml/min. Detection was set at a wavelength of 210 nm.

Calibration curve

A stock solution of the drug was prepared by dissolving 100 mg of clarithromycin in a 100 mL volumetric flask containing mobile phase, sonicated for about 10 min and then made up to the volume with same. Aliquots of these stock solutions were suitably diluted with mobile phase to get the working standard solution of drug in the concentration range between 80 and 120 μg/mL.

Analytical Method validation

The analytical method was validated for its precision, recovery, specificity and robustness studies.

Formulation and preparation of matrix tablets

Nine batches of clarithromycin tablets were prepared by using methocel K4M and methocel K100M as polymeric matrix forming material. Formulations were made by wet granulation technique using PVP and ethyl cellulose. Two different stages of preparation were employed based on the in vitro release profile. In the first procedure HPMC polymer was added to the dried granules as external phase and compressed into tablets. Clarithromycin was dry mixed with MCCP in a planetary mixer for 5 min and granulated with PVP and dried in hot air oven at 50°C for 3 hr. The dried granules were blended for 5 minutes with methocel, sodium starch glycollate, aerosol and talc. Finally magnesium stearate was added and blended for 2 minutes and compressed in a 16-station rotary tabletting machine. Based on the in vitro release results, methocel had been included as internal phase in the remaining formulations. The compressed tablets were film coated with HPMC 6 cps, titanium dioxide, talc, PEG 6000 and quinoline yellow lake as colorant. The composition of the formulations is shown in Table I.

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<th>F6</th>
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Drug-exciipient interaction studies

Pre-formulation studies are very important for the successful formulation of any dosage form. Fourier Transform Infrared Spectroscopy (FTIR) was used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with polymers, diluents and lubricants used in the tablet formulations. The earlier investigations recommended that 1:1 ratio of drug excipients maximizes the possibility of interaction and helps in easier detection of incompatibilities (Loganathan et al., 2003). Therefore, in the present study 1:1 ratio was used for the preparation of physical mixtures and analyzed for compatibility studies.

FTIR transform infrared

FTIR studies are very helpful in the evaluation of drug–polymer interaction studies. Incompatibility between the drugs and excipients can be predicted based on their characteristic wave numbers. Drug and various polymers were thoroughly mixed with 300 mg of potassium bromide, compressed and the IR spectrum was obtained between 450 and 4000 cm⁻¹ by placing the thin pellet in light path.

Evaluation of tablet formulations (Banker and Anderson, 1987)

Evaluation of characteristics of powder blend and tablets

The various characteristics of powder blend like angle of repose, bulk density, tapped density, compressibility index, Hausner’s ratio and drug content were studied. The formulated tablets were evaluated for hardness, friability, uniformity of weight and drug content.

Drug content of formulated tablets

Five tablets from each formulation were randomly chosen, pulverized and weight equivalent to 100 mg of clarithromycin was extracted with 100 ml phosphate buffer (pH 6.0). Aliquot from subsequent filtered solution was further diluted in phosphate buffer (pH 6.0) in such a way that theoretical concentration was same as that of standard concentration. Resultant solutions were analyzed in triplicate and the average results were taken.

In vitro dissolution studies

The dissolution studies were performed in triplicate for all the batches in a USP XXIII dissolution rate test apparatus (Type II). The release studies were performed in two different dissolution mediums. In the first method phosphate buffer pH 6.0 (dissolution medium I) was used and the dissolution studies were carried out for 2 hours. In the second method phosphate buffer pH 6.8 containing 0.5% sodium lauryl sulphate (dissolution medium II) was used and the dissolution studies were carried out for 24 hours.

Five milliliters aliquots were withdrawn at predefined intervals, and the volume of the dissolution medium was maintained by adding the same volume of fresh prewarmed dissolution medium and the drug release was analyzed.

Stability studies

The formulation which showed best in vitro release was selected for stability studies. The accelerated stability studies were conducted according to the ICH guidelines for a period of 6 months.

Results and Discussion

Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists need to acquire a better understanding of the physicochemical and biological parameters pertaining to their performance. Despite tremendous advantages in drug delivery the oral route remains the preferred route for the administration of therapeutic agents because of the low cost of therapy and ease of administration lead to high levels of patient compliance. It also remains the most popular and successful route for controlled delivery of drugs because of convenience and greater flexibility in dosage form.

Calibration curve of clarithromycin was found to be linear in the concentration range between 80 and 120 µg/mL, the correlation coefficient was found to be 0.999. The results show that an excellent correlation existed between peak area and concentration of drug within the concentration range tested. The retention time was around 7.8 min. The chromatogram is shown in Figure I.

This method was also validated for its intra-day and inter-day precision, the results indicated the good precision of the method. The specificity of the method was confirmed by comparing the Retention time of standard with that of the marketed formulation. There is no interference from the excipients commonly present in the tablet, which indicates that the excipients did not interfere with the estimation of the drug in the HPLC method. Hence this method is specific and selective. Recovery studies were performed by adding known amount of drug solutions to the pre-analyzed sample solutions and the recovery ranged from 99.15 % to 99.43%. The obtained results suggested the accuracy of the method for the determination of the clarithromycin in the formulation.

The standard deviation of peak areas was calculated for each parameter such as small changes in the variations of pH of the mobile phase (± 0.1), mobile phase composition (± 2.0%), wavelength of detection (± 5.0 nm) and flow rate (± 10.0% of absolute value). The % R.S.D. was found to be less than 2%. The low values of % R.S.D. indicated robustness of the method.

Compatibility studies were carried between the drug and the common excipients by FTIR techniques. Clarithromycin contains characteristic primary aromatic, amino, cyclic, ether and carboxylic groups, shows the values around 3469, 2976, 2939, 1731, 1691 and 1109 cm⁻¹. Infrared studies reveal that all characteristic bands around 3469, 2976, 2939, 1731, 1691 and 1109 cm⁻¹ were present in all spectra. While no new bands or shift in characteristic peaks appeared. The FTIR results revealed that there is no interaction between the drug and the excipients used in the formulation.
Fig. 1. HPLC chromatogram of standard clarithromycin.

Direct compression technique is not always feasible for hydrophilic matrix formulation containing methocel products; whereas in wet granulation process low-shear or higher shear granulation techniques can be adopted. Wet granulation technique can avoid the segregation of components in powder mix and provide better product flow on tablet press, overall improved tablet physical characteristics and uniform drug content within the dosage form.

The dried powder mixtures were tested for powder properties like angle of repose (between 25.13 and 31.12°), bulk density (between 0.55 and 0.74 g/cc), tapped density (between 0.66 and 1.88 g/cc), percentage compressibility index (between 15.46 and 19.13 g/cc) and Hausner’s ratio (between 1.10 and 1.31). The evaluation results revealed that all the powder mixture had good flow properties.

The formulated tablets were evaluated for its physical properties like thickness, weight variation, hardness, friability, and content uniformity. The thickness was found to be 7.0 and 7.4; weight variation 1.8 and 2.8%; hardness 9.8 – 11.3 kg/m² and friability 0.55 and 0.85% whereas the content uniformity was found to be 99.30 and 99.65% w/w. All the tablets were found to pass the uniformity of weight. The hardness of tablets from all formulations was between 9.8 and 11.3 kg/cm². All the formulations showed friability between 0.55 and 0.85% indicating that the tablets could withstand the mechanical shock. The evaluation results revealed that all the formulations were within the USP limits.

The performance of sustained release formulation has been reported to be greatly affected by physicochemical properties of polymer. Nine different combinations of controlled release matrix tablets of clarithromycin were prepared. In vitro release studies were carried out in two different dissolution mediums and compared with the USP limits. Formulation F1 and F2 showed more than 90% of the drug release in dissolution medium I in 45 min. This may be due to less quantity of polymer not able to retard the release; hence hydrophilic polymer amount was increased in the next formulation. Formulation F3 showed 93.1% drug release in dissolution medium I in 2 h whereas 87.8% drug release in dissolution medium II, still the desired drug release was not achieved hence modification was made in the polymer concentration. Formulation F4 showed 65.4% of drug release in dissolution medium I in first 30 min whereas 37.6% drug release in dissolution medium II in 2 h. The individual linearity of tablets and dissolution release profile was not satisfactory hence modification was made in the polymer concentration. Formulation F5 showed 95% drug release in dissolution medium I in first 1 h whereas 90% drug release in dissolution medium II in 12 h. The increased drug release in dissolution medium I may be due to increased polymer concentration leads to sudden burst of polymeric matrix and the linearity of individual tablets were not within the limit. So in the next formulations, polymer was added into the internal phase instead of adding in the external phase. Formulation F6 showed 98.2% drug release in dissolution medium I in 2 hr whereas 94.9% drug release in dissolution medium II in 24 h.

The drug release was improved satisfactorily than previous formulation but not satisfying the USP limit, hence modification was made in the polymer concentration. Formulation F7 showed 78% drug release in dissolution medium I in 2 hr whereas 74.55% drug release in dissolution medium II in 24 h. This release retard may be due to presence of sodium carboxy methyl cellulose and ethyl cellulose as binder, hence next trial was done without sodium carboxy methyl cellulose. Formulation F8 showed 99% drug release in dissolution medium I in 2 hr whereas 98.2% drug release in dissolution medium II in 24 h still the desired drug release as per USP limit was not achieved hence modification was made in the next trial. Formulation F9 showed 97.6% drug release in dissolution medium I in 2 hr whereas 98.6% drug release in dissolution medium II in 24 h. The release profile was found to be within the USP limits.
The release results are shown in Figure 2 and 3. Comparative dissolution profile between the optimized formulation and market formulation is shown in Figure 4 and 5. The difference factor (f1) and similarity factor (f2) were found to be 2.44 and 83.18 for dissolution medium I; 1.44 and 89.71 for dissolution medium II. The above results indicate that the in vitro release profile was comparable.

Stability studies were carried out at 40°C and 25°C and tested for its physical properties and in vitro release studies, stability study results revealed that the prepared formulation was stable in the stress condition.

Conclusions
The study shows that the matrix method can be employed for preparing clarithromycin sustained release formulation using combination of hydrophilic polymers like Methocels and sodium carboxy methyl cellulose. It was concluded that the formulation F9 which consist of 30 mg of sodium carboxy methyl cellulose along with other ingredients provided a release that was comparable with the marketed formulation. The developed analytical method was validated which showed high specificity and precision. The F9 formulation was stable at different stress conditions. The difference and similarity factors were found to be comparable for F9 and marketed formulations in the both dissolution media.

References

Address correspondence to: T.N.K. Suriyaprakash, Dept of Pharmaceutics, Al Shifa College of Pharmacy, Perintalmanna, Kerala – 679 322, India.
E-mail: tnksuri@gmail.com